

WHAT IS CLAIMED IS:

1. An isolated GPRA polypeptide comprising an amino acid sequence that has at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13 and 15 over the entire length of the selected SEQ ID NO. when compared using the BLASTP algorithm with a wordlength (W) of 3, and the BLOSUM62 scoring matrix.
2. The isolated GPRA polypeptide of claim 1 comprising an amino acid sequence selected from the group consisting of B-Long (SEQ ID NO: 5), B-Short (SEQ ID NO:7) , C (SEQ ID NO:9), D (SEQ. ID NO:11), E (SEQ ID NO:13) and F (SEQ ID NO:15) provided that up to 34 amino acids can be substituted, deleted or inserted relative to the selected SEQ ID NO.
3. The isolated GPRA polypeptide of claim 1 comprising the amino acid sequence selected from the group consisting of B-Long (SEQ ID NO: 5), B-Short (SEQ ID NO:7) , C (SEQ ID NO:9), D (SEQ. ID NO:11), E (SEQ ID NO:13) and F (SEQ ID NO:15)
4. An isolated GPRA polypeptide comprising at least 10 contiguous amino acids from amino acids 343-377 of B-long (SEQ ID NO:5).
5. An isolated GPRA polypeptide comprising an amino acid sequence that has at least 80% sequence identity to an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13 and 15 over a sequence comparison window of at least 40 amino acids when compared using the BLASTP algorithm with a wordlength (W) of 3, and the BLOSUM62 scoring matrix provided that the polypeptide includes a variant amino acid encoded by a variant form shown in Table 7.
6. An isolated GPRA polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:3 provided that the sequence contains an amino acid substitution of Asn 107Ile, Arg241Ser, or Gln344Arg.
7. An isolated GPRA polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:5 provided that the sequence contain as an amino acid substitution of Asn instead of Ile at codon position 107, Arg instead of Ser at codon position 241, and/or Thr instead of Ile at codon position 366.

8. An isolated nucleic acid encoding the GPRA polypeptide of any of the preceding claims.

9. The isolated nucleic acid of claim 8 that hybridizes under highly stringent conditions to any of SEQ ID NOS: 4, 6, 8, 10, 12, and 14 wherein the highly stringent conditions are $6 \times \text{NaCl/sodium citrate (SSC)}$ at about 45°C for a hybridization step, followed by a wash of $2 \times \text{SSC}$ at 50°C

10. An isolated nucleic acid of claim 8 that hybridizes under highly stringent conditions to any of SEQ ID NOS: 1, 4, 6, 8, 10, 12, and 14 without hybridizing under the same highly stringent conditions to SEQ ID NO:2, wherein the highly stringent conditions are $6 \times \text{NaCl/sodium citrate (SSC)}$ at about 45°C for a hybridization step, followed by a wash of $2 \times \text{SSC}$ at 50°C .

11. An isolated nucleic acid of claim 8 having a sequence that is at least 90 % identical to a nucleic acid having a sequence selected from the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, and 14 over the entire length of the selected SEQ ID NO when compared using the BLASTN algorithm with a wordlength (W) of 11, $M=5$, and $N=-4$.

12. An isolated nucleic acid of claim 8 having a sequence that is at least 80 % identical to a nucleic acid having a sequence selected from the group consisting of SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 over a sequence comparison window of at least 100 nucleotides when compared using the BLASTN algorithm with a wordlength (W) of 11, $M=5$, and $N=-4$ provided that the nucleic acid includes a polymorphic site occupied by a variant form as shown in Table 3 or Table 7.

13. The isolated nucleic acid of claim 12, wherein the variant form is at a polymorphic site not designated by a * in Table 7.

14. An isolated nucleic acid of claim 8 having a sequence that is at least 80 % identical to a nucleic acid having a sequence selected from the group consisting of SEQ ID NO: 1, 2, 4, 6, 8, 10, 12, and 14 over a sequence comparison window of at least 100 nucleotides when compared using the BLASTN algorithm with a wordlength (W) of 11, $M=5$, and $N=-4$ provided that the nucleic acid includes a polymorphic site occupied by a reference form designated with a * in Table 7.

15. An isolated genomic DNA molecule or a minigene having at least one intronic sequence and encoding a GPRA polypeptide that has at least 80 % sequence identity to an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13 and 15 over a region at least 40 amino acids in length when compared using the BLASTP algorithm with a wordlength (W) of 3, and the BLOSUM62 scoring matrix .

16. The isolated genomic DNA molecule or minigene of claim 15, comprising at least exons III-IV of SEQ ID NO: 2.

17. The isolated genomic DNA molecule or minigene of claim 15, wherein the intronic sequence is from intron 2 or 3 of a GPRA gene.

18. The isolated genomic DNA molecule or minigene of claim 15, wherein the GPRA polypeptide includes amino acids 343-377 of B-Long (SEQ ID NO:5)

19. The isolated genomic DNA molecule or minigene of claim 15, wherein the polypeptide is SEQ. ID NOS: 3, 5, 7, 9, 11, 13 or 15.

20. The isolated nucleic acid, genomic DNA molecule or minigene of any of claims 8-19, linked to a second nucleic acid with which it is not naturally associated.

21. The isolated nucleic acid, genomic DNA molecule or minigene of claim 20, wherein the second nucleic acid includes a heterologous promoter operably linked to a gene within the isolated nucleic acid.

22. A vector comprising the isolated nucleic acid, genomic molecule or minigene nucleic acid of any of claims 8-21.

23. A host cell comprising the vector of claim 22.

24. An antibody that specifically binds to an epitope within amino acids 343-377 of B-long (SEQ ID NO:5) or amino acids 332-366 of B-short (SEQ ID NO:7).

25. A method of preventing or treating asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer, comprising

administering to a patient suffering from or at risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer an effective amount of a

modulator of a GPRA polypeptide comprising an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13, and 15.

26. The method of claim 25, further comprising administering an effective amount of a modulator of a AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

27. The method of claim 25, wherein the modulator binds to the GPRA polypeptide.

28. The method of claim 25, wherein the modulator inhibits expression of the GPRA polypeptide.

29. The method of claim 25, wherein the modulator is a transcript of an AAA1 gene or an inhibitor of expression of an AAA1 gene.

30. The method of claim 26, wherein the modulator of the AAA1 polypeptide binds to the AAA1 polypeptide.

31. The method of claim 26, wherein the modulator of the AAA1 polypeptide inhibits expression of the AAA1 polypeptide.

32. A method of identifying a modulator of a GPRA polypeptide, comprising

contacting a cell expressing a GPRA polypeptide with an agent;
determining whether the agent modulates expression of the GPRA polypeptide and/or signal transduction through the GPRA polypeptide, wherein the GPRA polypeptide is defined by any of claims 1-7.

33. The method of claim 32, wherein the cell further expresses an AAA1 polypeptide.

34. A method of determining risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer, comprising;

determining whether the individual has a variant polymorphic form in a GPRA gene, wherein presence of the variant polymorphic form indicates risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

35. The method of claim 34, wherein the variant form occurs in a noncoding region of the GPRA gene

36. The method of claim 34, wherein the variant form occurs in a coding region of the GPRA gene

37. The method of claim 34, wherein the variant form occurs between introns 1 and 4 of the GPRA gene.

38. The method of claim 34, wherein the determining comprises determining whether the individual has a variant form relative to SEQ ID NO: 1 (AST-1 locus).

39. The method of claim 34, wherein the determining comprises determining whether the individual has a variant form relative to any of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, and 15.

40. The method of claim 34, wherein the variant form is a variant form shown in Table 3.

41. The method of claim 40, wherein the variant form is at a polymorphic site shown in Table 3.

42. The method of claim 34, wherein the variant form is a variant form shown in Table 7.

43. The method of claim 34, wherein the variant form is a variant form at a polymorphic site not designated * in Table 7.

44. The method of claim 34, wherein the determining comprising determining whether the individual has variant polymorphic forms relative to SEQ ID NO:1 at each of a plurality of polymorphic sites within the AST-1 locus, the presence of variant polymorphic forms at two or more of the plurality of polymorphic sites indicating increased risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

45. The method of claim 34, further comprising determining whether the individual has a variant polymorphic form in an AAA1 gene, wherein presence of the variant

polymorphic form indicates risk of asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer.

46. The method of claim 45, wherein the variant polymorphic form occurs in the coding region of the AAA1 gene.

47. The method of claim 34, further comprising amplifying at least part of SEQ ID NO:1 (AST-1) locus including the polymorphic site before the determining step.

48. The method of claim 34, wherein the determining is performed by allele specific amplification, allele specific hybridization, single strand conformation polymorphism (SSCP), oligonucleotide ligation assay, single-base extension assay, or restriction fragment length polymorphism (RFLP).

49. A method for identifying a polymorphic site correlated with a disease selected from the group consisting of asthma, other IgE-mediated disease, chronic obstructive pulmonary disease and cancer or susceptibility thereto, comprising;

identifying a polymorphic site within a GPRA gene,
determining whether a variant polymorphic form occupying the site is associated with the disease or susceptibility thereto.

50. The method of claim 49, wherein the variant form occurs in a noncoding region of the GPRA gene

51. The method of claim 49, wherein the variant form occurs in a coding region of the GPRA gene

52. The method of claim 49, wherein the variant form occurs between introns 2 and 4 of the GPRA gene.

53. The method of claim 49, wherein the determining comprises determining whether the individual has a variant form relative to SEQ ID NO: 1 (AST-1 locus)

54. The method of claim 49, wherein the determining comprises determining whether the individual has a variant form relative to any of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, and 15.

55. The method of claim 49, wherein the determining is performed by comparing the frequency of the variant polymorphic form in individuals with and without the disease.

56. A primer or probe nucleic acid that hybridizes under highly stringent conditions to a segment of SEQ ID NO:1, 2 or 4 or a variant form thereof differing from SEQ ID NO: 1, 2 or 4 at a position shown in Table 3 or Table 7, wherein the segment includes or is immediately adjacent to a polymorphic site shown in Table 3 or Table 7.

57. The primer or probe of claim 56, wherein the position is a position other than a position designated * in Table 7.

58. The primer or probe of claim 56 that is perfectly complementary to a segment of SEQ ID NO:1, 2 or 4.

59. The primer or probe of claim 56 that is perfectly complementary to a variant form of a segment of SEQ ID NO:1, 2 or 4 shown in Table 3 or Table 7.

60. The primer or probe of claim 56 that specifically hybridizes to the segment of SEQ. ID NO: 1, 2 or 4 without hybridizing to a corresponding segment of an allelic variant shown in Table 3 or Table 7.

61. A primer of claim 56 for conducting a single-base extension reaction, whereby the primer is perfectly complementary to a segment that is immediately adjacent to but does not include the polymorphic site.

62. A transgenic animal comprising a nucleic acid according to any one of claims 8-21.

63. The transgenic animal of claim 62, further comprising a nucleic acid encoding an AAA1 polypeptide.

64. A transgenic animal of claim 62 disposed to develop a characteristic of asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer in

which an endogenous a GPRA gene encoding a cognate form of a GPRA polypeptide defined by any of SEQ ID NOS: 3, 5, 7, 9, 11, 13 and 15 is functionally disrupted to prevent expression of a gene product.

65. The transgenic animal of claim 64 in which an endogenous AAA1 gene encoding a cognate form of an AAA1 polypeptide defined by an of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41 is functionally disrupted to prevent expression of a gene product of the AAA1 gene.

66. A kit for use in diagnosing or assessing predisposition to asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer, comprising;

a container; and in the container:

a compound, preferably labeled, capable of detecting a polymorphic form at a polymorphic site in a susceptibility locus for asthma as defined by SEQ ID NO:1, 2 or 4.

67. The kit according to claim 66, wherein the polymorphic site occurs at a position shown in Table 3, Table 7, Table 12, Table 13 or Table 14.

68. The kit according to claim 66, wherein the compound is a primer or probe.

69. The kit according to claim 66, wherein said primer is the primer of claim 56.

70. An isolated AAA1 polypeptide comprising an amino acid sequence that has at least 80% sequence identity to an amino acid sequence selected from the group consisting of SEQ. ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41 over the entire length of the selected SEQ ID No: when compared using the BLASTP algorithm with a wordlength (W) of 3, and the BLOSUM62 scoring matrix.

71. The isolated AAA1 polypeptide of claim 70 comprising an amino acid sequence that has at least 90% sequence identity to the selected amino acid sequence.

72. The isolated AAA1 polypeptide of claim 70 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

73. The isolated AAA1 polypeptide of claim 70 comprising at least 10 contiguous amino acids from an amino acid sequence selected from the group consisting of SEQ ID NOS:17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

74. An isolated nucleic acid encoding the AAA1 polypeptide of any of claims 70-73.

75. The isolated nucleic acid of claim 74 that hybridizes under highly stringent conditions to any of SEQ ID NOS: 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40, wherein the highly stringent conditions are $6 \times \text{NaCl/sodium citrate (SSC)}$ at about 45°C for a hybridization step, followed by a wash of $2 \times \text{SSC}$ at 50°C

76. An isolated nucleic acid of claim 74 having a sequence that is at least 80% identical to a nucleic acid having a sequence selected from the group consisting of SEQ ID NO: 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40 over the entire length of the selected SEQ ID NO when compared using the BLASTN algorithm with a wordlength (W) of 11, M=5, and N=-4.

77. The isolated nucleic acid of claim 76, wherein at least one polymorphic site shown in Table 12 is occupied by a variant nucleotide.

78. An isolated nucleic acid having at least 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOS:16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40.

79. An isolated genomic DNA molecule or a minigene having at least one intronic sequence and encoding an AAA1 polypeptide that has at least 80 % sequence identity to an amino acid sequence selected from the group consisting of SEQ. ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41 over the entire length of the selected SEQ ID NO. when compared using the BLASTP algorithm with a wordlength (W) of 3, and the BLOSUM62 scoring matrix .

80. The isolated genomic DNA molecule or minigene of claim 79, wherein the polypeptide has a sequence selected from the group consisting of SEQ. ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

81. The isolated nucleic acid, genomic DNA molecule or minigene of claim 79 or 80 linked to a second nucleic acid with which it is not naturally associated.

82. The isolated nucleic acid, genomic DNA molecule or minigene of claim 79, wherein the second nucleic acid includes a heterologous promoter operably linked to a gene within the isolated nucleic acid.

83. A vector comprising the isolated nucleic acid, genomic molecule or minigene nucleic acid of any of claims 74-82.

84. A host cell comprising the vector of claim 83.

85. An antibody that specifically binds to a polypeptide selected from the group consisting of SEQ ID NOS:17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

86. A method of preventing or treating asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer, comprising administering to a patient suffering from or at risk of asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer an effective amount of a modulator of an AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ. ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

87. The method of claim 86, wherein the modulator binds to the AAA1 polypeptide.

88. The method of claim 86, wherein the modulator inhibits or induces expression of the AAA1 polypeptide.

89. A method of identifying a modulator of an AAA1 polypeptide, comprising

contacting an AAA1 polypeptide with an agent;

determining whether the agent binds to the AAA1 polypeptide, modulates expression of the AAA1 polypeptide or modulates activity of the AAA1 polypeptide, wherein the AAA1 polypeptide comprises an amino acid sequenced as defined by any of SEQ ID NOS:17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41.

90. The method of claim 89, wherein the AAA1 polypeptide is expressed from a cell.

91. A method of determining risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer, comprising;
determining whether the individual has a variant polymorphic form in an AAA1 gene, wherein presence of the variant polymorphic form indicates risk of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

92. The method of claim 91, wherein the variant form occurs in a noncoding region of the AAA1 gene

93. The method of claim 91, wherein the variant form occurs in a coding region of the AAA1 gene

94. The method of claim 91, wherein the determining comprises determining whether the individual has a variant form relative to SEQ ID NO: 1 (AST-1 locus)

95. The method of claim 91, wherein the determining comprises determining whether the individual has a variant form relative to any of SEQ ID NOS: 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40.

96. The method of claim 91, wherein the variant form is a variant form shown in Table 12.

97. The method of claim 91, wherein the determining is performed by allele specific amplification, allele specific hybridization, single strand conformation polymorphism (SSCP), oligonucleotide ligation assay, single-base extension assay, or restriction fragment length polymorphism (RFLP).

98. A method for identifying a polymorphic site correlated with a disease selected from the group consisting of asthma, other IgE mediated disease, chronic obstructive pulmonary disease or cancer or susceptibility thereto, comprising;

identifying a polymorphic site within an AAA1 gene,
determining whether a variant polymorphic form occupying the site is associated with the disease or susceptibility thereto.

99. The method of claim 98, wherein the variant form occurs in a noncoding region of the AAA1 gene.
100. The method of claim 98, wherein the variant form occurs in a coding region of the AAA1 gene
101. The method of claim 98, wherein the determining comprises determining whether the individual has a variant form relative to SEQ ID NO: 1 (AST-1 locus)
102. The method of claim 98, wherein the determining comprises determining whether the individual has a variant form relative to any of SEQ ID NOS: 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40.
103. The method of claim 98, wherein the determining is performed by comparing the frequency of the variant polymorphic form in individuals with and without the disease.
104. A primer or probe nucleic acid of nucleotides that hybridizes under highly stringent conditions to a segment of SEQ ID NO: 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40 or a variant form thereof differing from SEQ ID NOS.16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40 at a single polymorphic site.
105. The primer or probe of claim 104, wherein the polymorphic site is one shown in Table 3 or 12.
106. The primer or probe of claim 104 that is perfectly complementary to a segment of SEQ ID NOS:16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40.
107. A primer or probe of claim 104 for conducting a single-base extension reaction, whereby the primer is perfectly complementary to a segment that is immediately adjacent to but does not include the polymorphic site.
108. A transgenic animal comprising a nucleic acid according to any one of claims 74-82.
109. A transgenic animal of claim 108 disposed to develop a characteristic of asthma, other IgE-mediated disease, chronic obstructive pulmonary disease or cancer in

which an endogenous a AAA1 gene encoding a cognate form of an AAA1 polypeptide defined by any of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41 is functionally disrupted to prevent expression of a gene product.

110. A pharmaceutical composition comprising an effective amount of a GPRA polypeptide comprising an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13, and 15 or a modulator thereof for the prevention or treatment of asthma or other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

111. The pharmaceutical composition of claim 110, further comprising an effective amount of an AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, and 41 or a modulator thereof.

112. The pharmaceutical composition of claim 110, wherein the modulator binds to the GPRA polypeptide and/or activates/inhibits expression of the GPRA polypeptide.

113. The pharmaceutical composition of claim 111, wherein the modulator is a transcript of an AAA1 gene or an activator/inhibitor of expression of an AAA1 gene.

114. The pharmaceutical composition of claim 111, wherein the modulator binds to the AAA1 polypeptide and/or activates/inhibits expression of the AAA1 polypeptide.

115. Use of a GPRA polypeptide comprising an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, and 13 or a modulator thereof for the manufacture of a medicament for the prevention or treatment of asthma or other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

116. The use of claim 115, wherein a GPRA polypeptide comprising an amino acid sequence selected from the group consisting of SEQ. ID NOS: 3, 5, 7, 9, 11, 13, and 15 or a modulator thereof, and an AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, and 41 or a modulator thereof are used for the manufacture of said medicament.

117. A pharmaceutical composition comprising an effective amount of an AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, and 41 or a modulator thereof for the prevention or treatment of asthma or other IgE mediated disease, chronic obstructive pulmonary disease or cancer.

118. The pharmaceutical composition of claim 117, wherein the modulator binds to the AAA1 polypeptide and/or activates/inhibits expression of the AAA1 polypeptide.

119. Use of an AAA1 polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, and 41 or a modulator thereof for the manufacture of a medicament for the prevention or treatment of asthma or other IgE mediated disease, chronic obstructive pulmonary disease or cancer.